201-15756

Distillation by-products from manufacture of 2-ethyl-1-hexanol

CAS Number 68909-68-7

A Variable Mixture Also Know as:

- 2-Ethylhexanol distillation residuum
- 2-Ethylhexanol heavies
- EP-204
- Oxoel 800

U.S. EPA HPV Challenge Program Submission

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Executive Overview

The high-boiling fraction from the manufacture of 2-ethyl-1-hexanol CAS no. 68609-68-7 is known by several names in commerce including the more generic name "2-Ethylhexanol Heavies" as well as the more specific names "EP-204" (in the United States) and "Oxoel 800" (in Germany) that are used by BASF to designate this particular byproduct, which is called EP-204 in this document. EP-204 is a clear, pale yellow to green liquid with a mild characteristic odor. Most of the product is utilized for its heat value as a fuel and a portion is used in ore flotation applications. Annual production of EP-204 by BASF in the United States is estimated to be 3 to 5 million pounds and is limited to one plant. Production is in a closed system with storage in closed tanks. Shipping is limited to bulk transport by rail car or tank truck. Occupational exposure in manufacture is restricted by the use of essentially closed systems for production. Inhalation and dermal exposure during sampling and loading is controlled by the use of personal protective equipment. Inhalation exposure is also limited by low volatility. Available compositional information and the chemistry involved in the genesis of EP-204 are discussed in detail to understand the composition and possible components, and this information is used to conduct a hazard assessment of the material based on its known and possible components.

Some physicochemical, fate and toxicity studies have been conducted with commercial EP-204 and/or Oxoel 800. Studies have also been conducted on pure compounds and mixtures similar enough to EP-204 that they provide information relevant to defining the physicochemical properties and potential environmental and health effects of this mixture. EP-204 has a melting point of about -62°C and a boiling point range of about 180-350°C. Its vapor pressure at 20°C is 1-5 hPa and the components have log $K_{o/w}$ values ranging from about –0.48 to 5.17. Water solubility of the components ranges from less than 1 to greater than 1000 mg/L. Data on EP-204 itself indicates that it is 70% biodegradable in 28 days on an OECD 301B test; however, some components would probably be better characterized as inherently biodegradable. Examination of the major components indicate that the mixture is water stable, but components would be rapidly degraded in the atmosphere by indirect photolysis with a half-life from about 3 to 20 hours. If released into the environment in water it is expected to distribute primarily to water and sediment.

Hazard to aquatic organisms was estimated from the known aquatic toxicity of the major components. Based on the components it is estimated that this material will have low aquatic toxicity with EC_{50} values in the range of 3 to 100 mg/L. The limited solubility and high biodegradability also reduce environmental concern. Octanol-water partition coefficients were located or estimated for all identified components comprising 1% or more of the mixture. The log $K_{o/w}$ values (–0.48 to 5.17) combined with biodegradability and likely rapid metabolism indicate little propensity for bioaccumulation. Probable pathways of mammalian metabolism are discussed in detail; most pathways are similar to the metabolism of fatty nutrients to carbon dioxide.

EP-204 demonstrated an acute LD_{50} greater than 5000 mg/kg after oral gavage administration to rats of each sex. Oral toxicity data from components support an assessment of low acute toxicity. Saturated vapor exposure of rats

for 7 hours did not result in mortality or other significant clinical signs of toxicity. Acute dermal toxicity hazard is considered low based on data from representative components. No repeated administration studies are available for EP-204; however, several of its major components have been tested. Data from subchronic oral and inhalation testing of 2-ethylhexanol were selected as the most appropriate surrogate data to estimate the repeated-dose hazard of EP-204. Based on these data, EP-204 will probably cause peroxisome proliferation at high oral doses in the rat, but administration will be associated with few other effects at daily oral doses of 250 mg/kg or less. By inhalation exposure, no adverse effects are anticipated up to its saturation concentration in air. Repeated dose data from other components support an assessment of low repeated-exposure hazard.

Potential genetic effects were assessed via examination of adequate data for most of the major components of EP-204. The weight of evidence indicates lack of mutagenic or clastogenic activity for components of EP-204. No structural alerts were identified for any of the untested known components. Based on the chemistry, analysis of components by GC/MS and functional group analysis (by carbon-13 NMR), none of the unidentified components are anticipated to have genotoxic activity.

Lack of reproductive toxicity was indicated by the lack of effects on reproductive organs in repeated dose studies of components and surrogates and the lack of developmental toxicity for 2-ethylhexanol. In addition, no reproductive toxicity was observed in a one-generation dietary reproduction study of di-2-ethylhexyl adipate, which is another surrogate for EP-204 components.

Lack of developmental toxicity was also indicated by a National Toxicology Program gavage study with 2-ethylhexanol in mice where developmental toxicity was not observed at the highest dose tested (194 mg/kg-day). The dermal administration of 2-ethylhexanol to rats did not result in developmental toxicity even in the presence of maternal toxicity. A one-generation dietary reproduction study of di-2-ethylhexyl adipate in rats reported minor fetotoxicity at maternally toxic doses with a developmental NOAEL equivalent to ~ 120 mg/kg-day 2-ethylhexanol. In addition, the oral and dermal administration of another surrogate chemical, 2-ethyl-1,3-hexanediol, did not result in developmental toxicity below maternally toxic doses.

In summary, although this is a complex and variable mixture, enough is known about its chemistry and overall composition to derive a well-informed hazard characterization based on adequate studies of EP-204, components and surrogates. There is sufficient confidence in the hazard assessment to consider all the U.S. EPA HPV program data elements as being filled. No additional testing is recommended.

Testing Plan and Rationale

Testing Plan in Tabular Format

CAS No. 68609-68-7 EP-204	Information Available?	OECD Study ?	GLP Study?	Supporting Information?	Estimation Method?	Acceptable?	Testing Recommended?	
HPV Endpoint								
Physical Chemical								
Melting Point	Y	N	N	Y	N	Y	N	
Boiling Point	Y	N	N	Y	N	Y	N	
Vapor Pressure	Y	N	N	Y	Y	Y	N	
Partition Coefficient	Y	N	N	N	Y	Y	N	
Water Solubility	Y	N	N	N	Y	Y	N	
Environmental & Fate								
Photo-Degradation	Y	N	N	N	Y	Y	N	
Water Stability	Y	N	N	Y	Y	Y	N	
Transport	Y	N	N	N	Y	Y	N	
Biodegradation	Y	Y	N	Y	N	Y	N	
Ecotoxicity								
Acute Fish	Y	N	N	Y	N	Y	N	
Acute Invertebrate	Y	N	N	Y	N	Y	N	
Acute Algae	Y	N	N	Y	N	Y	N	
Toxicity								
Acute	Y	N	?	Y	N	Y	N	
Repeated Dose	Y	N	Y	Y	N	Y	N	
Genetic Toxicology *"in vitro"*	Y	N	Y	Y	N	Y	N	
Genetic Toxicology "*in vivo*"	Y	N	N	Y	N	Y	N	
Reproductive	N	N	N	Y	N	Y	N	
Developmental	Y	Y	Y	Y	N	Y	N	

Introduction

The high-boiling fraction from the manufacture of 2-ethyl-1-hexanol CAS no. 68609-68-7 is known by several names in commerce including the more generic name "2-Ethylhexanol Heavies" and the more specific name "EP-204" used by BASF to designate this particular byproduct. The TSCA Inventory refers to this material as "1-Hexanol, 2-ethyl-, manuf. of, by-products from, distn. Residues" with the following description:

> The complex combination of hydrocarbons produced by the distillation of products from a 2-ethyl-1-hexanol manufacturing process. It consists predominantly of organic compounds such as alcohols, aldehydes, esters, carboxylic acids and acetals having carbon numbers predominantly in the range of C4 through C16 and boiling in the range of 199°C to 308°C (390°F to 586°F).
>
> Unknown, Variable, Complex, Biological Flag: UVCB

The TSCA Inventory description above is chemically broad, which is accurate in this case, as some of the actual components in this mixture have never been identified. Additionally, the TSCA definition allows for variations of the manufacturing process. In the case of the BASF material EP-204, the process used to produce 2-ethylhexanol is dimerization of n-butyraldehyde in the presence of base, hydrogen and a catalyst. The initial reaction is an aldol condensation that is followed by reductive dehydration and hydrogenation to produce 2-ethylhexanol. Although conditions are optimized to maximize the yield of 2-ethylhexanol, other reactions occur and the 2-ethylhexanol must be separated from by-products by fractional distillation. The material that is left behind from this distillation is the residue, often called "bottoms" or "heavies", from the distillation. Because this is a generic name for a product that could be produced using various ratios of feedstocks and even different chemical processes, the definition for CASNO 68609-68-7 is intentionally broad and somewhat vague. Although the BASF production is restricted to a single process, the byproducts remain variable because the primary objective of the chemistry is to produce maximal yields of high-purity 2-ethylhexanol. Consistency of byproduct composition is a secondary consideration.

Another variable is that the product is made both in the United States and in Germany. The German byproduct is called Oxoel 800 and it is nominally produced under the same conditions as US manufactured EP-204. The overall composition of Oxoel 800 is very similar to EP-204, and within the confines of the official TSCA definition for this CAS Registry Number, but the ratios of components may differ between US and German production at any given time. Other variables that apply to both the US and German production are that the distillation conditions can be temporarily modified to accommodate different purity grades of 2-ethylhexanol; and the activity of the catalyst decreases with time, which can alter distribution of products. The TSCA UVCB flag (Unknown, Variable, Complex, Biological Flag) applies well to this mixture, as it is an indeterminate mixture of chemicals some of which have not been definitively identified. As this document is written based on BASF production, conclusions may not be fully representative of CASNO 68609-68-7 in its broadest sense. For simplicity, the material called EP-204 in this document encompasses the Oxoel 800 produced in Germany but may not represent all variations of composition allowed under the TSCA definition of CASNO 68609-68-7.

EP-204 is a clear, pale yellow to green liquid with a mild characteristic odor (1). Industrial and commercial applications are listed as a "chemical solvent"; however, much of the product is utilized for its heat value as a fuel and a portion is used in ore flotation applications. Estimated annual production of EP-204 by BASF in the United States is in the range of 3 to 5 million pounds. United States production of the material is limited to one plant.

Production is in a closed continuous flow reaction system with product storage in closed tanks. Shipping is limited to bulk transport by rail car or tank truck. Occupational exposure in manufacture is restricted by the use of essentially closed systems for production. Inhalation and dermal exposure are possible during sampling and loading/unloading of rail cars/tank trucks but is controlled by the use of personal protective equipment when handling the material outside of the closed manufacturing system.

The composition of EP-204 is a critical aspect of this HPV analysis; thus, the chemistry of EP-204 formation and its typical composition are reviewed in detail in the "chemistry" section of this document.

Some physicochemical, fate and toxicity studies have been conducted with commercial EP-204 and/or Oxoel 800. Studies have also been conducted on pure compounds and mixtures similar enough to EP-204 that they provide information relevant to defining the physicochemical properties and potential environmental and health effects of EP-204. Studies on EP-204 and on appropriate surrogates are briefly reviewed in this testing rationale document, which also describes how these studies meet the SIDS (Screening Information Data Set) end-points of the United States Environmental Protection Agency (USEPA) High Production Volume Challenge (HPV) program. Robust summaries have been prepared for key studies; supporting studies are referenced in these summaries or given as shorter summaries using the IUCLID format. Where specific studies on EP-204 or Oxoel 800 have not been conducted, data from studies of major components or other surrogates are provided to fill the HPV endpoints. In some cases where calculated data are acceptable, a calculation based on the major components has been utilized for the SIDS parameter in question. The use of acceptable surrogates and adequate estimation methods are encouraged by the U.S. EPA and other regulatory authorities to avoid unnecessary testing cost and animal usage.

Chemistry

EP-204 (CASNO 68609-68-7) is an indeterminate mixture of variable composition derived as a byproduct from a chemical process. To appreciate how this material relates to other mixtures and pure chemicals that have relevant data and to comprehend the potential range of various components, it is valuable to understand the process and process variables that contribute to the production of this byproduct mixture.

EP-204 is a residue remaining from the aldol dimerization and dehydration of butyraldehyde under strongly basic conditions followed by hydrogenation in the presence of hydrogen and a catalyst. The intended reaction is addition of one butyraldehyde molecule to another to produce a transient alcohol that dehydrates to 2-ethylhexenal. The 2-ethylhexenal is reduced under these conditions to give 2-ethylhexanol – the desired product. Under the conditions employed, various side reactions occur to produce alternate materials, many of higher

molecular weight than 2-ethylhexanol. During the distillation phase of this continuous process, additional chemical reactions may occur to cause further condensation reactions of various components into higher molecular weight compounds through dehydration reactions. As the higher molecular weight compounds tend to be less volatile, they remain in the in the residue from the distillation. These distillation residues comprise EP-204.

The primary and intended reaction is an aldol condensation followed by reduction:

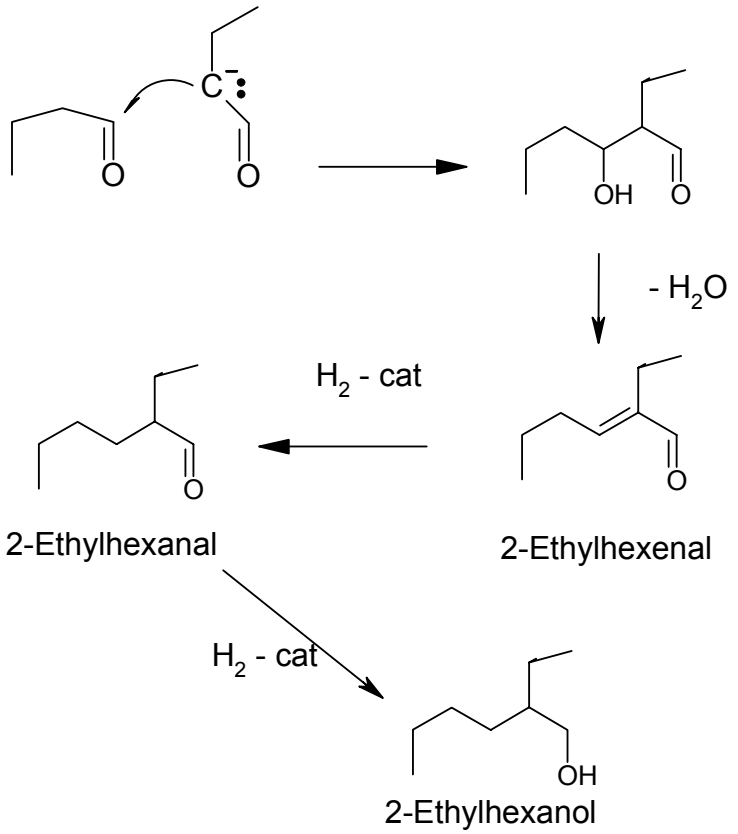

Figure 1. Intended Reaction to form 2-Ethylhexanol

In addition to this intended series of reactions, side reactions occur, such as addition of the butyraldehyde carbanion to 2-ethylhexanal to produce a 12-carbon compound. The number of potential byproducts is large, accounting for the complexity of EP-204 and the reason that some components remain unidentified. Chemistry of byproduct formation is discussed later in this testing plan. Table 1 gives the nominal range of chemicals, mostly as classes, comprising EP-204.

EP-204 Chemical Components	Weight % Approximate range
2-Ethylhexan-1-ol	2-15
Alcohols, C12 and higher	5-15
Diols, C8, C12 and higher	25-50
Alkyl ethers	2-20
Alkyl esters	5-15
Aliphatic hydrocarbons	5-7
Aliphatic aldehydes	0-2
Aliphatic acetals	0-5

Table 1. Categories of Components in EP-204

Additional characterization work has been conducted to categorize some of the individual components and the following components were identified by chromatographic techniques.

Chemical Component	CAS No.	Weight % Approx range
2,4-Diethyloctane-1,5-diol* (C12)	94277-83-5	5-40
2-Ethyl-1,3-hexanediol	94-96-2	5-15
2,4-Diethyloctane-1-ol		5-15
2-Ethylhexanol	104-76-7	5-15
2-Ethylhexenal	645-62-5	0-10
2-Ethylhexanal	123-05-7	0-10
n-Butyl-n-butyrate	109-21-7	1-5
2-Ethylhexyl-1,3-dibutyrate		0-4
n-Butanol	71-36-3	0-2
n-Butyraldehyde	123-72-8	0-2
2-Ethylhexyl-butyl ether	62625-25-6	0-5
* Tentative ID, could also be 2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol based on possible chemistry		

Table 2. Typical Composition of EP-204 (identified components)

In addition to this chromatographic characterization, a ^{13}C-NMR spectrum was recorded on current production material (specifically for this HPV submission) to gain assurance that the bulk product is composed of all aliphatic materials and to quantitate any aromatic carbons that might be present. The spectrum is shown as Figure 2; and it can be seen that there is a lack of aromatic carbons, further confirming the homogeneity of the material

regarding its aliphatic character. This indicates that cyclic- or polycylic-aromatic compounds are not present in the product.

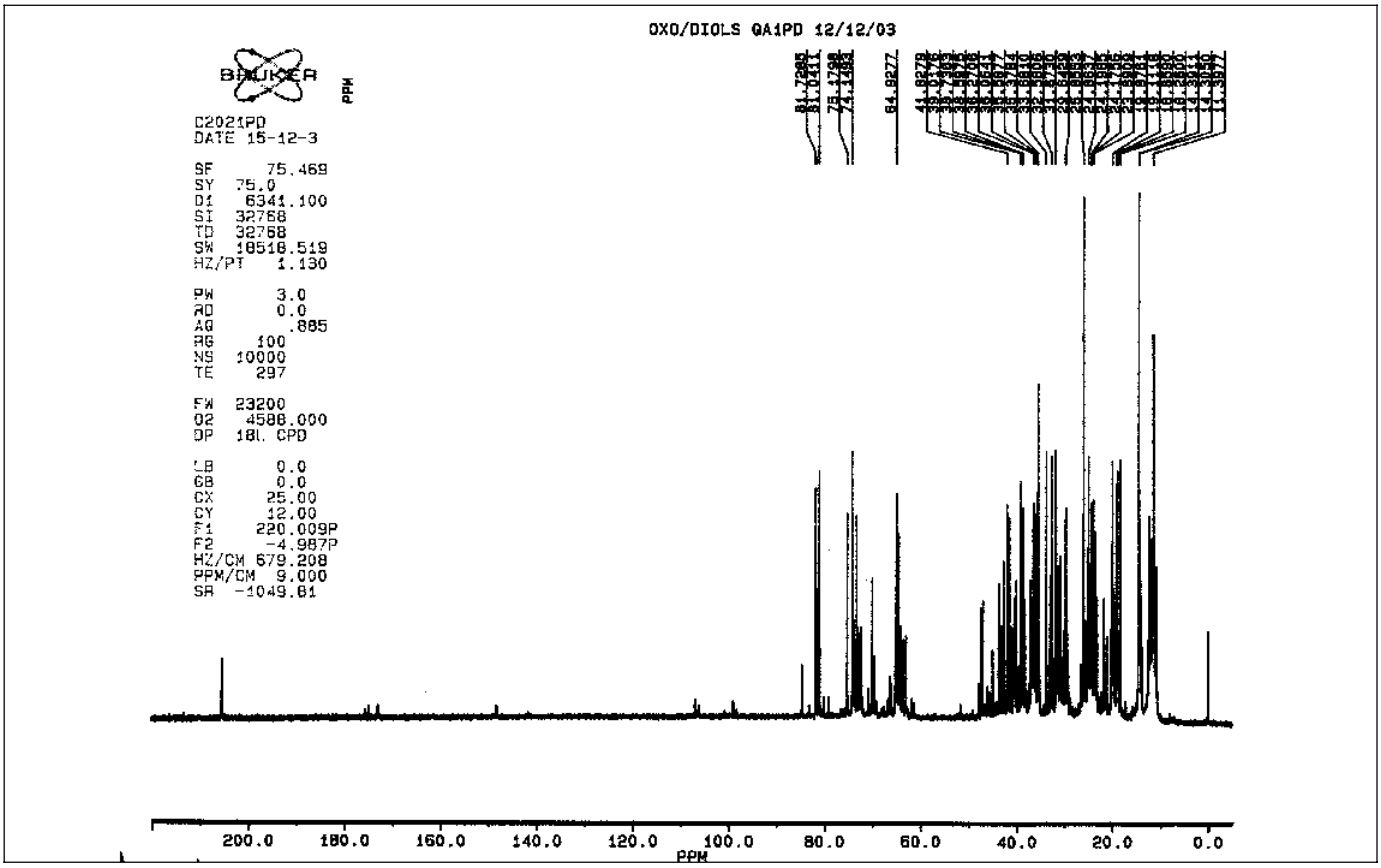

Figure 2. Carbon-13 NMR Spectrum of E-204

Tentative assignment of some of the carbon signals in this recent production run of EP-204 is useful in assessing the variety of structures contained in this mixture. It should be kept in mind that this is a sample of recent United States production at a particular time for this variable mixture and is not necessarily representative of all production.

The higher field lines (larger ppm chemical shifts) represent functional groups and quantitation (the nmr methodology is considered semi-quantitative) was derived from integration of the spectrum and has been normalized on the basis of 8-carbon units. The total percentage (on the basis of total carbon) of material containing functional groups (acetals, alcohols, esters and ethers) is a range of 70 to 110% with the remainder (0 to 30%) representing any saturated-hydrocarbon signals that are buried in the methylene and methyl carbon signals (Table 3).

Chemical Shift (ppm)	Tentative Identification	Approx Relative Percent
206	Aldehyde	< 5% of C8 groups
170-180	Esters	< 5% of C8 groups
99-108	Acetals, ethers	< 5% of C8 groups
80-82	Hindered alcohols or ethers	10-15 % of C8 groups
74-76	Ethers (1° or 2°) Alcohols (2°)	20-30 % of C8 groups
62-66	Alcohols (1°)	40-50 % of C8 groups
10-45	Saturated hydrocarbons [plus hydrocarbon chains of components, such as 2-EH]	Remainder

Table 3. Composition Based on NMR Data

Although this is only a semi-quantitative assessment of a "snapshot" sample we learn that the main category of component is primary alcohols with a significant contribution of secondary alcohols and/or ethers and very little material that could be characterized as an aldehyde or ester. This is consistent with the expected chemistry of the reaction system and, since one objective of the reaction is to convert an aldehyde to an alcohol (also a facile chemical reaction), we expect little free aldehyde or ester (also reducible) in the byproduct. Because the alcohols and ethers that are formed are stable to the reaction conditions, these molecules become "trapped" in the reaction mixture and do not undergo further reaction under these conditions. A consideration of the expected chemical reactions in this system provides further insight into the genesis and nature of EP-204 components.

Figure 3 shows the intended reaction and the probable genesis of some of the possible C-8 and C-12 diols. 2,4-Diethyloctane-1,3-diol, 3-ethyl-3-propyl-4-hydroxymethylhexane-1-ol and similar higher molecular mass compounds could be formed as shown by 1,2- or 1,4-addition of the butyraldehyde carbanion to 2-ethylhexenal. The reverse addition, where a carbanion derived from 2-ethylhexenal adds to butyraldehyde would be expected to generate yet another isomeric 12-carbon diol (2,4-diethyl-1,5-octanediol) as shown in Figure 4.

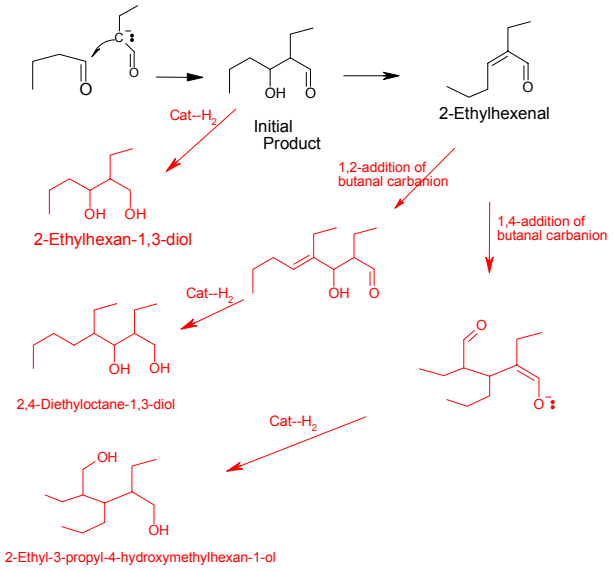

Figure 3. Formation of some C-8 and C-12 diols in EP-204

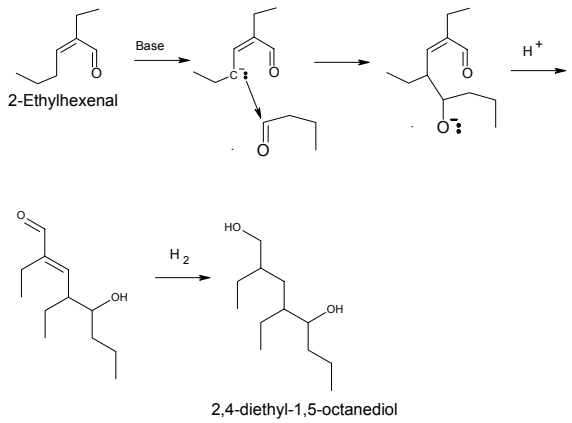

Figure 4. Possible Mechanism of 2,4-Diethyl-1,5-octanediol Formation

Analysis of some German production runs of material have indicated that as much as 40% of the mixture can be 2,4-diethyloctane-1,5-diol. This identification, however, is not unequivocal as isomeric materials with the same molecular mass and similar physicochemical properties, 2,4-diethyloctane-1,3-diol or 3-ethyl-3-propyl-4-hydroxymethylhexane-1-ol, could also account for this GC peak, or the peak could be a mixture of these isomers.

Figure 5 depicts the probable genesis of higher molecular weight diols in EP-204. The β-hydroxyaldehyde initial product from the aldol condensation loses water rapidly to produce 2-ethylhexenal. Although 2-Ethylhexenal is an intended intermediate in the production of 2-ethylhexanol, if it undergoes an addition reaction before it can be reduced it gives a 12-carbon intermediate that can in turn either be reduced or added to again with another 4-carbon unit to give the 16-carbon intermediate. This intermediate can likewise be reduced or add yet another 4-

carbon unit and so on. Moreover, it is possible to combine an 8-carbon carbanion derived from 2-ethylhexenal or 2-ethylhexanal (as in Figure 4) with a 12 or 16-carbon dialdehyde. The number of potential structures is large.

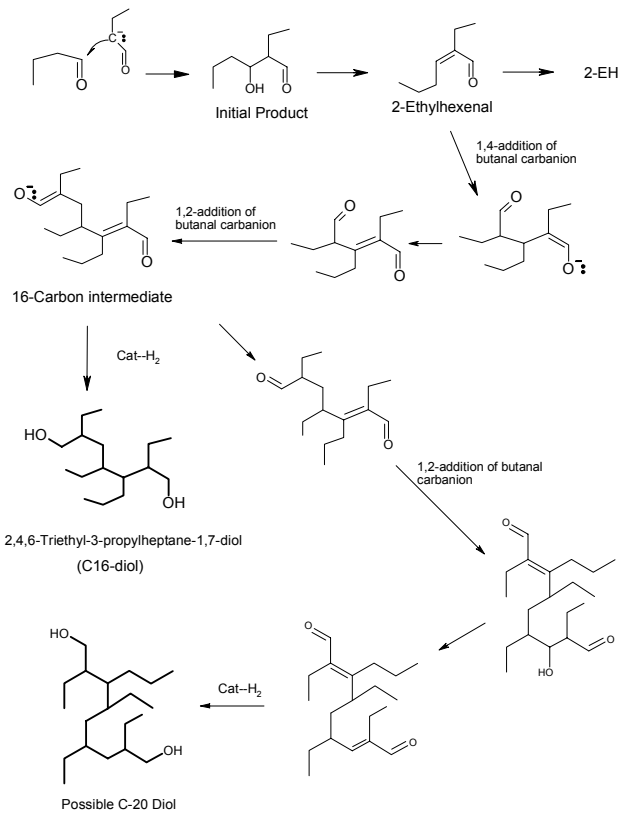

Figure 5. Potential Higher Diols Formation.

GC-Mass spectral analysis of a typical EP-204 sample, however, indicates (BASF internal data) that structures with carbon backbones greater than 12 carbons are not found at levels greater than one about percent of the mixture, as shown in Figure 6. Mass spectral analysis based on the molecular ion is a good indicator of the molecular weight of the components but cannot discriminate structural isomers without authentic chemical samples to use as standards; therefore, the structures labeled as "isomer" in Figure 6 represent only one possible structural isomer of the component with that empirical formula.

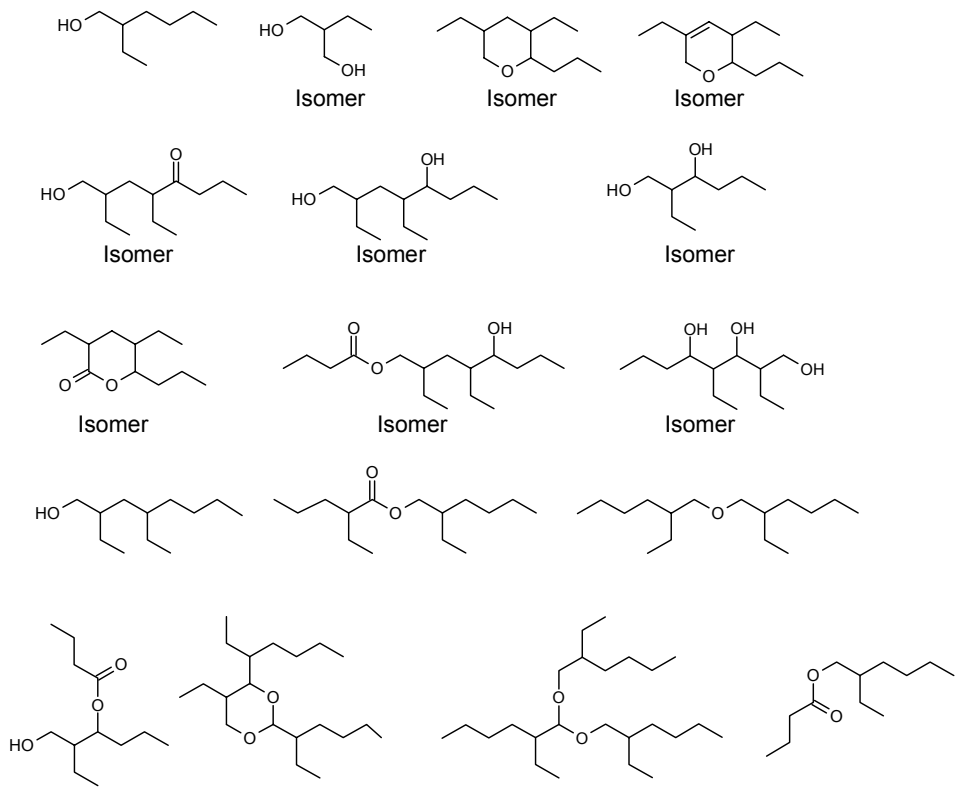

Figure 6. GC-MS Identification of All Components Above 1% in EP-204.
The structures marked "isomer" indicate that this is just one of several structural formulas for a material with this empirical formula

2,4-Diethyloctane-1-ol is another component that can be formed after dehydration of the initial product to 2-ethylhexenal followed by an aldol condensation. In some samples of German production material this byproduct has been identified at levels up to 10%. In Figure 7, two reaction paths that lead to its formation are depicted. This can be formed either by carbanion addition to 2-ethylhexenal (the initial dehydration product) or by carbanion addition to 2-ethylhexanal, which is formed by partial reduction of the α,β-unsaturated aldehyde. The exact mechanism of formation is irrelevant and is probably dependent on the activity of the hydrogenation catalyst. Of additional interest in this pathway is the intermediates A and B, which are both capable of 1,2 or 1,4 carbanion addition reactions leading to yet more byproduct structures.

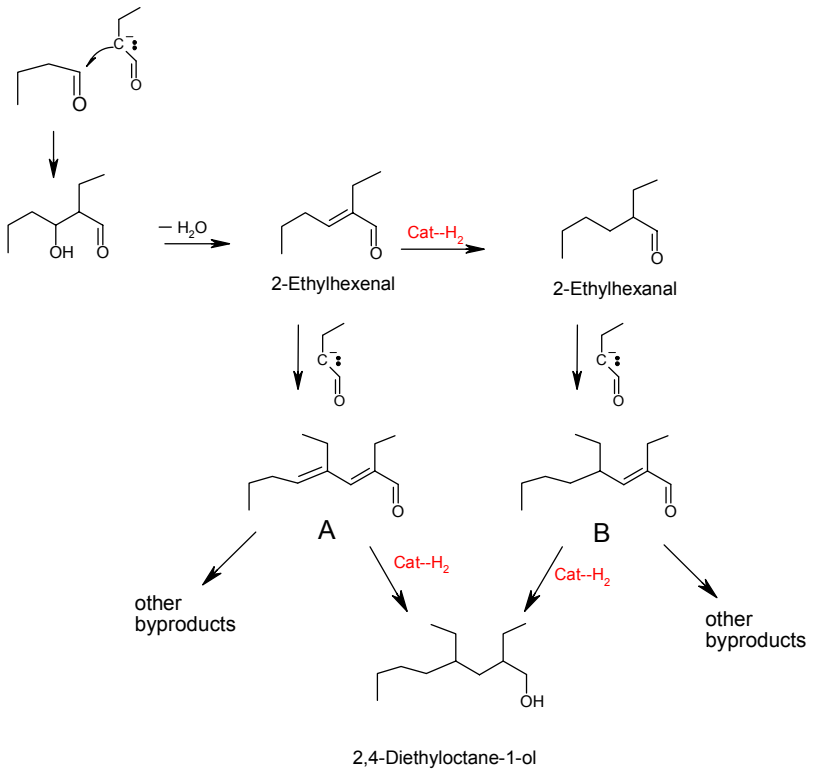

Figure 7. Mechanisms of 2,4-Diethyloctane-1-ol Formation.

What can be concluded by examination of the carbanion addition reactions (aldol condensations) is that this non-specific chemistry can produce numerous configurations of the carbon skeleton including diastereomeric isomers when the carbon skeleton reaches 12 carbons or greater and two or more asymmetric centers are present.

Figure 8 gives the presumed mechanism for ether formation and specific examples of probable ether structures that are expected under these reaction conditions. These structures are probably formed but may distill off the residue during the removal of 2-ethylhexanol leaving only higher molecular weight ethers such as di-2-ethylhexanol ether which was detected by GC-MS

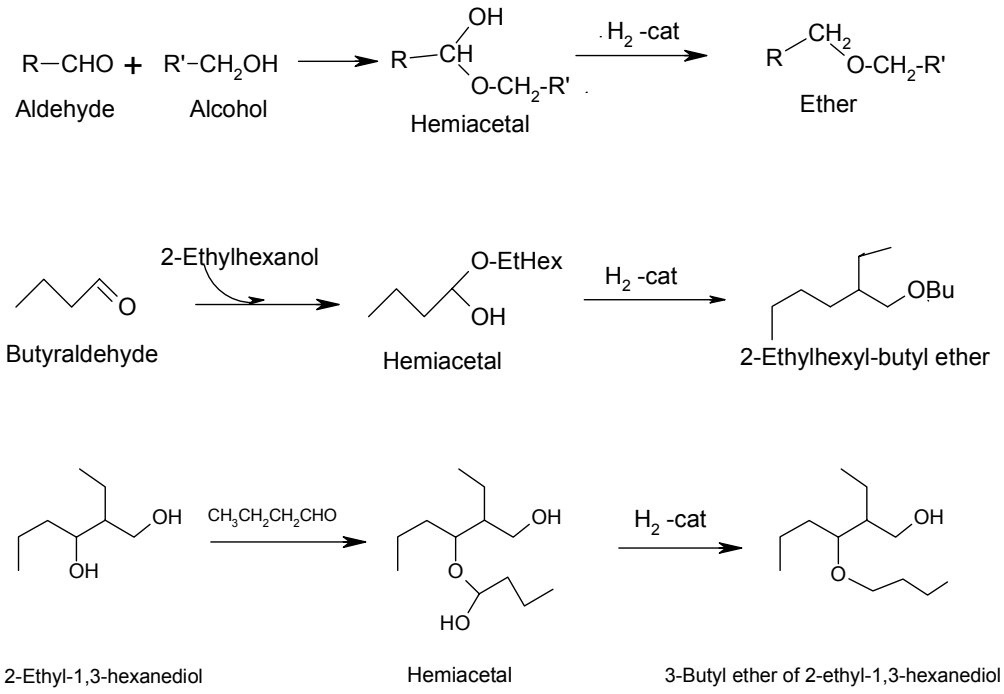

Figure 8. Ether Formation in EP-204

The last chemistry figure (Figure 9) gives the presumed mechanism for acetal formation and a specific example of a probable acetal formed in the reactions that could become a component of EP-204 but was not identified in the mass spectral analysis.

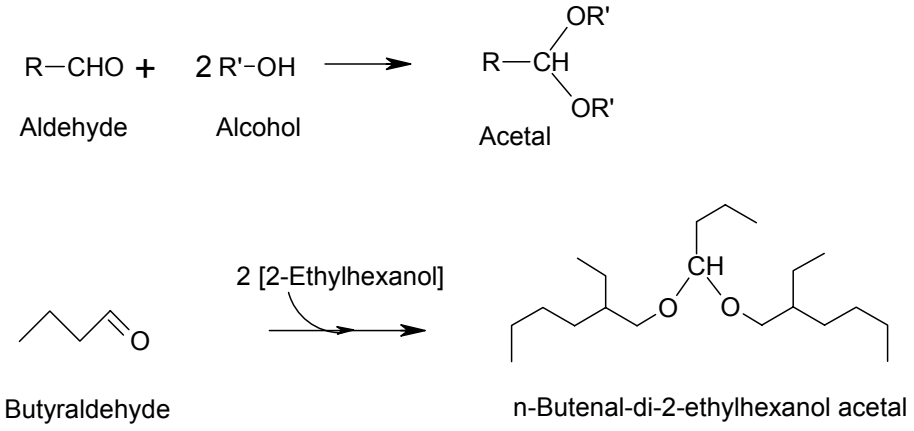

Figure 9. Acetal formation in EP-204

In summary, through carbon-13 and GC-MS characterization of current production material and through detailed consideration of the intended reactions and likely side reactions we have established that there is considerable structural diversity expected in both the size and configuration of the carbon skeleton. In addition, functional

groups produced in the reaction can be alcohols, ethers, acetals and esters. We have also established from the carbon-13 spectrum that alcohols (mono and diols) are currently the most prevalent functional group and based on the intended reaction (alcohol production) it is expected that alcohols will remain the prevalent species in EP-204 as reaction conditions undergo continual optimization to improve yield of 2-ethylhexanol. Thus, for the HPV hazard assessment of this material, it is logical to concentrate on the alcohols as the prime determinant of hazard unless there is reason to believe that one of the quantitatively lower level functional group categories is highly toxic, and as there is no rationale for that, the focus of hazard assessment for EP-204 will be on the alcohols which make up the bulk of the product.

Physicochemical Data

Physicochemical data for EP-204 are available from manufacturer's information and from EPIWIN estimates and are summarized in Table 4.

Melting Point	ca. –62˚ C (1, 2)
Boiling Point	ca. 180-350° C @ 1013 hPa (1, 2, 3)
Vapor Pressure	1 – 5 hPa @ 20˚ C (4)
Partition Coefficient	Variable Log $K_{o/w}$ = -0.48 to 5.17 (5)
Water Solubility	Variable, <1 to >1000 mg/L (5)

Table 4: Physicochemical Summary Data for EP-204

The melting point and boiling point range are measured properties for EP-204 (1, 2) and for Oxoel 800 (3) (which is the material produced by the same process in Germany by BASF). The boiling point is given as a wide range, typical of a material that undergoes fractional distillation as it boils. Likewise the freezing point is a measured property for typical production material but is expected to vary due to the variable composition.

A single octanol-water partition coefficient cannot be defined as this mixture has a variety of components that have individual hydrophobicities. To understand the potential distribution and bioaccumulative properties of EP-204, individual components must be taken into consideration. Table 5 contains the EPIWIN estimated log $K_{o/w}$ for the most prevalent components with concentrations estimated to be greater than 1% of the mixture. In addition to being the materials that actually make up most of EP-204, they represent a good cross section of the chemical classes that make up EP-204 and are considered representative of the entire sample (6). The $K_{o/w}$ spans from –0.48 for butyraldehyde to 5.17 for 2-ethylhexyl-1,3-dibutyrate. Although six of the materials have $K_{o/w}$ values equal to

or greater than 3 (indicating that bioaccumulation is possible), the one with the highest $K_{o/w}$ is an ester that is expected to be both biodegradable and easily metabolically converted by man and animals to a diol with a $K_{o/w}$ of 1.6 (see table). Most of the other components with high hydrophobicity are alcohols that are expected to be rapidly biodegraded in the environment and, if absorbed, can be metabolically conjugated to increase excretion. The only exception from the list below is the ether, 2-ethylhexyl-n-butyl. It is, however, a minor component (1% range) and expected to be inherently biodegradable and metabolically susceptible to oxidative transformation at a rate inconsistent with bioaccumulation.

Component	SMILES	log Kow*	H_2O Sol* (mg/L)
2-Ethylhexanol	CCCCC(CC)CO	2.73 c	880 e
2-Ethylhexenal	CCCC=C(CC)C=O	2.62 c	548.6 e
2-Ethylhexanal	CCCCC(CC)C=O	2.71 c	400 e
n-Butanol	CCCCO	0.88 e	63,200 e
2-Ethyl-1,3-hexanediol	CCCC(O)C(CC)CO	1.60 c	4,200 e
2-Ethylhexyl-1,3-dibutyrate	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	5.17 c	0.567 e
n-Butyl-n-butyrate	CCCC(=O)OCCCC	2.83 c	309 c
n-Butyraldehyde	CCCC=O	-0.480 e	2385 e
2,4-Diethyloctane-1-ol	CCCCC(CC)CC(CC)CO	4.62 c	18.7 c
2,4-Diethyloctane-1,5-diol	CCCC(O)C(CC)CC(CC)CO	3.49 c	44.4 c
2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol (C12-diol)	CCC(CO)C(CCC)C(CO)CC	3.49 c	44.4 c
2,4,6-Triethyl-3-propylheptane-1,7-diol (C16-diol)	CCC(CO)CC(CC)C(CCC)C(CO)CC	4.89 c	1.69 c
2-Ethylhexyl-butyl ether	CCCCC(CC)COCCCC	4.90 c	3.32 c
* e = experimental value from SRC database, c = calculated value using EPIWIN			

Table 5: Water Solubility and Octanol-Water Partition Coefficients for EP-204

The vapor pressure of EP-204 is another variable parameter. Its initial vapor pressure will depend on the vapor pressure of the most volatile component and its physicochemical interactions with other components in the mixture. As the proportion of chemical components is variable, the initial vapor pressure will also be variable. In addition, as the mixture evaporates and loses the more volatile components, the nominal vapor pressure will decrease. The vapor pressure of typical bulk material was estimated from the initial boiling point using chemical principles (see robust summary). In the environment after dispersal, each component's individual vapor pressure will be a determinant in distribution of the chemical. Because of this, measured or estimated individual vapor pressures were used in the fugacity calculations describing hypothetical distribution. These individual component vapor pressures are available in the fugacity calculations given in the robust summary for distribution (see robust summaries).

Water solubility is dependent on both the water solubility of individual components and on the bulk properties of the material as a whole in equilibrium with water. When an organic liquid phase is present in water, the partition coefficient of an individual component is as important as its water solubility. In addition, with any partially water-soluble mixture, cosolvent effects are expected to play an important role. As EP-204 is a variable composition mixture and cosolvent effects are difficult to model, the experimental or calculated water solubilities are given as reference values, but it must be kept in mind that under varying conditions the effective solubility could be higher or lower. In consideration of the EP-204 composition being mostly higher molecular weight low solubility components, the mixture overall is expected to display relatively low water solubility and will form two phases when mixed with water.

Recommendation: No additional physicochemical studies are recommended. The available data fill the HPV required data elements with sufficient precision to define the hazards of this variable composition material.

Environmental Fate and Pathways

Biodegradation potential has been determined using carbon dioxide evolution (OECD guideline 301B). EP-204 (tested as Oxooel 800) was found to be 70% biodegradable (as percent of theoretical carbon dioxide evolution) in 28 days (7). Although this indicates the material is biodegradable, the time required to achieve 60% biodegradation was not short enough to meet the definition of "readily biodegradable" by the OECD criteria. This information is consistent with the structures of the most prevalent compounds, many of which are considered readily biodegradable; however, some of the individual components with linear and branched ether structures are probably better characterized as "inherently biodegradable". Based on inspection of the chemical structures, no component is anticipated to be resistant to biodegradation.

Most of the components are considered stable to hydrolysis, as they do not contain a hydrolysable group. The major exception to this is the esters and although they are theoretically hydrolysable, they are predicted by the HYDROWIN Program (v1.67) to have half-lives grater than one year in water at pH 7 (Table 6).

Component	Total K_b (L/mol-sec)	Hydrolysis Half-live	
		pH 8.0	pH 7.0
2-Ethylhexyl-1,3-dibutyrate	3.561×10^{-2}	225 days	6.2 years
n-Butyl-n-butyrate	5.317×10^{-2}	151 days	4.1 years

Table 6. Predicted Hydrolytic Stability of Ester Components of EP-204

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The approach used was to take the most prevalent identified materials in the preparation and individually determine their reactivity with hydroxyl radical assuming each component will be unaffected by the others after vaporization into the troposphere. The program produced estimated rate constants ranging from 6.89×10^{-12} to 50.0×10^{-12} cm^3/molecule-sec. Using the default atmospheric hydroxyl radical concentration in APOWIN and the range of estimated rate constants of major components of EP-204 for reaction with hydroxyl radical, the estimated half-life of EP-204 vapor in air is approximately 3 to 20 hours. The full details of the calculations are given in the robust summaries and Table 7 provides a summary of the results from these calculations. Photodegradation of the lower level and unidentified components is expected to be facile; as these components have similar empirical formulas and functional groups, their rate constants for reaction with hydroxyl radical will be similar.

Component	SMILES	Results of AOP v 1.09 Hydroxyl Radical Reaction Prediction	
		Rate Constant ($x10^{12}$ cm/molec-sec)	Half-life (hrs)
2-Ethylhexanol	CCCCC(CC)CO	13.2	9.7
2-Ethylhexenal	CCCC=C(CC)C=O	50.0	2.6
2-Ethylhexanal	CCCCC(CC)C=O	34.0	3.8
n-Butanol	CCCCO	6.89	19
2-Ethyl-1,3-hexanediol	CCCC(O)C(CC)CO	22.2	5.8
2-Ethylhexyl-1,3-dibutyrate	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	17.5	7.3
n-Butyl-n-butyrate	CCCC(=O)OCCCC	10.6	12
n-Butyraldehyde	CCCC=O	25.4	5.0
2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol (C12-diol)	CCC(CO)C(CCC)C(CO)CC	24.5	5.2
2,4,6-Triethyl-3-propylheptane-1,7-diol (C16-diol)	CC(CO)CC(CC)C(CCC)C(CO)CC	29.3	4.4
2-Ethylhexyl-n-butyl ether	CCCCC(CC)COCCCC	35.1	3.7

Table 7. Summary of Photodegradation Estimates

As shown by the calculations (see robust summaries), the primary reaction for this series of components is hydrogen abstraction, the rate of which increases linearly as the number of hydrogen atoms in the molecule increase. The ether moiety activates adjacent hydrogen atoms toward radical abstraction while the ester has a deactivating influence giving the esters a longer predicted half-life. Based on the chemical structures of EP-204 components, reaction with ozone will not be important. In addition, none of the materials will absorb light above 290 nm; thus, direct photolysis in the troposphere will not be significant. In summary, all components are expected to have relatively short atmospheric half-lives reacting primarily with atmospheric hydroxyl radical.

Theoretical Distribution (Fugacity) of EP-204 in the environment was estimated using the MacKay EQC level III model in EPIWIN v 3.05 using release only to water, (considered the most likely situation) as the means of entry into the environment. The approach used was to take the ten materials known or expected to be in the in the mixture in the greatest quantity and individually determine their fugacity assuming that one component will not significantly affect the distribution of the other after dispersal. As the measured vapor pressure of EP-204 is a function of the partial pressures of each component, it is more appropriate to use the EPIWIN predicted vapor

pressure for each component in the calculation. Likewise, individual predicted values for log K_{ow}, K_{oc}, and half-lives were utilized. The biodegradation half-lives that were utilized were EPIWIN generated but were evaluated for consistency with the known biodegradability of the preparation and found to be representative.

The entire data set with the values utilized for all parameters is shown in the Robust Summary for distribution in the environment and a summary is shown in Table 8. The components evaluated are representative of the full spectrum of components contained in EP-204 and include alcohols, diols, aldehydes, an α,β-unsaturated aldehyde and esters. Examination of Table 8 reveals that the EP-204 components distribute primarily to water. The more volatile components have some distribution to air and 2-ethylhexyl-1,3-dibutyrate; 2,4-diethyloctane-1-ol and 2,4,6-triethyl-3-propylheptane-1,7-diol (the C16-diol) have significant predicted distributions in sediment. Soil distribution is not considered to be important for any component under these conditions of 100% release to water. Not apparent from this summary table, because the distribution is normalized to 100%, are the magnitude of initial loss of material to biodegradation in a waste-treatment plant and the relatively short half-lives of the components in the environment due to biodegradation and indirect photolysis.

Component	SMILES	Distribution (Percent)			
		Air	Water	Soil	Sediment
2-Ethylhexanol	CCCCC(CC)CO	0.52	98.9	0.02	0.52
2-Ethylhexenal	CCCC=C(CC)C=O	0.94	98.4	0.01	0.61
2-Ethylhexanal	CCCCC(CC)C=O	1.81	97.5	0.01	0.67
n-Butanol	CCCCO	2.55	99.6	0.02	0.16
2-Ethyl-1,3-hexanediol	CCCC(O)C(CC)CO	<0.1	99.8	0.01	0.22
2-Ethylhexyl-1,3-dibutyrate	CCCC(OC(=O)CCC)C(CC)COC(=O)CCC	0.03	55.5	0.01	44.4
n-Butyl-n-butyrate	CCCC(=O)OCCCC	4.51	94.9	0.03	0.56
n-Butyraldehyde	CCCC=O	1.07	98.7	0.01	0.18
2,4-Diethyloctane-1-ol	CCCCC(CC)CC(CC)CO	0.87	79.6	0.02	19.6
2,4-Diethyloctane-1,5-diol	CCCC(O)C(CC)CC(CC)CO	0.02	97.6	0.02	2.35
2-Ethyl-3-propyl-4-hydroxymethylhexan-1-ol (C12-diol-2)	CCC(CO)C(CCC)C(CO)CC	0.03	97.6	0.02	2.35
2,4,6-Triethyl-3-propylheptane-1,7-diol (C16-diol)	CC(CO)CC(CC)C(CCC)C(CO)CC	0.04	69.3	0.06	30.6
2-Ethylhexyl-n-butyl ether	CCCCC(CC)COCCCC	1.74	77.4	0.01	20.9

Table 8: Theoretical Distribution (Fugacity) of EP-204 **in the environment**

Recommendation: No additional fate and pathway studies are recommended. The available data fill the HPV required data elements.

Ecotoxicity

A guideline-compliant daphnia study has been conducted on an analyzed sample of EP-204 (test material was Oxoel 800) giving a 48-hour EC_{50} of 52 mg/L (8). Studies on fish and algae have not been conducted with the subject mixture; however, experimental data for invertebrates and algae are available for many of the major components of EP-204. Aquatic toxicity of other components can be estimated using ECOSAR and the appropriate QSAR model. It is believed that the aquatic toxicity of EP-204 can be adequately defined by the toxicity of its individual components and by the single daphnia test. The good correlation between the component-predicted toxicity and the empirical daphnia data (*vide post*) supports this methodology as a conservative means of assessing the aquatic toxicity of this substance.

Experimental and modeling data for aquatic toxicity of the major components of EP-204 are shown in Table 9. In addition to experimental data for all three throphic level endpoints on 2-Ethylhexanol; 2-Ethexenal; 2-Ethylhexeneal and n-Butanol, studies on fish (fingerling channel catfish) have been reported for 2-Ethylhexyl-1,3-diol in the EPA ECOTOX database indicating an LC_{50} of 624 mg/L for a 96-hour exposure. Studies on daphnia or green algae, however, were not located in the open literature for this component.

Aquatic Toxicity (mg/L)						
	2-EH	2-Ethexenal	2-Ethexanal	n-Butanol	2-Ethylhexyl-1,3-diol	C-12 diol
Fish, 96-hr LC_{50}	17-30 (9)[§]	6.0 (10)	8 (11)	> 1000 (12)	257* [624][†]	6.0*
Daphnia, 48-hr EC_{50}	39 (9)	20 (13)	11.5 (14)	> 1000 (12)	268*	7.1*
Algae, 96-hr EC_{50}	10-20 (9)	19.3 (15)	52 (14)	> 100 (12)	164*	4.8*

§ Numbers in parentheses are references.

* Estimated using ECOSAR (16)

[†] Experimental LC_{50} of 624 mg/L reported in EPA ECOTOX database (17)

Table 9: Aquatic Toxicity of EP-204 Components.

Determination or estimation of the actual ecotoxicity values and the actual solubility of EP-204 under environmental conditions is complicated by the fact that it is a variable composition mixture and, in addition, potential environmental conditions are variable. The aldehydes, which are expected to be more toxic to aquatic species than the neutral organics (based on the ECOSAR specific aldehydes model), tend to be minor components of this mixture. Examination of the composition Tables 1, 2 and 3 (*vide ante*) indicates that the major components are alcohols and diols, with a high proportion of C-8 and C-12 carbon chains. Modeling and experimental data included in Table 9 indicate that the diols are less toxic to aquatic life than the mono-alcohols and that the C-8 diol is of low toxicity and the C-12 is probably moderately toxic.

If the components are lumped together, assuming no specific joint-toxic action and the same mechanism of action, a rough estimate of the toxicity of EP-204 can be calculated using the principle of additivity. This is done by

summing the component's fraction divided by the LC_{50} or EC_{50}, dividing this by the sum of the fractions and taking the reciprocal. The L/EC_{50} values used are the experimental or estimated single values or the geometric mean if a range of L/EC_{50} values is given in Table 9. The calculation for the estimated LC_{50} for fish is given below as an example. All calculations are given in the attached robust summaries.

Example Calculation of Estimated LC_{50} for Fish				
Component	[%]	LC_{50} (mg/L)	$1/LC_{50}$	x[%]
2,4-Diethyloctane-1,5-diol* (C12)	22.5	6.0	0.166667	3.75
2-Ethyl-1,3-hexanediol	10	257	0.003891	0.038911
2-Ethylhexanol	10	24.4	0.040984	0.409836
2-Ethylhexenal	5	6	0.166667	0.833333
2-Ethylhexanal	5	8	0.125	0.625
n-Butanol	1	1000	0.001	0.001
%Total	[53.5]		Σ	5.65808
		Div Tot [%]		0.105759
		1/x = Estimated LC_{50}		9.5

The Estimated LC_{50} or EC_{50} for fish, daphnids and algae are:

- Fish 9.5 mg/L
- Daphnids 13 mg/L
- Green Algae 9.3 mg/L

Realistically, given the variability of the bioassays used to determine the toxicity of the individual components and the variability of the mixture, a range for these LC_{50} and EC_{50} values of 3 to 100 mg/L is considered probable for EP-204. As a test of these calculations, there are experimental Daphnia magna data showing a 48-hour EC_{50} of 52 mg/L (8). This is certainly in the range suggested above but about 5 fold higher than the calculated value; however, it was remarked in the laboratory report that the test substance was "not completely soluble in the tested concentration range".

Analysis of the EP-204 lot (test material was Oxoel 800) used to expose Daphnia is shown in Table 10. In addition, the table contains columns giving the experimental (e) or predicted (p) water solubility and the experimental (e) or predicted (p) daphnia 48-hour EC_{50} for each component. The final column is the calculated concentration of each individual component at a concentration of 50 mg/L (the EC_{50}) of the whole material.

Examination of Table 10 reveals that at the EC_{50} of 52 mg/L, all the identified major components are predicted to be fully soluble; however, some may have partitioned into the small amount of insoluble material observed in the test vessel. The insoluble material may be high molecular weight components from the "high-boiling components". It can be concluded that a typical sample of EP-204 is of low toxicity to daphnia in spite of the

ECOSAR prediction of a lower LC_{50} due to the presence of diethyloctanol in this particular sample at 5 to 10%. It is further concluded that these components do not have an apparent synergistic activity on one another and estimation of aquatic toxicity for this mixture by estimation from the components is a conservative way to evaluate the aquatic hazard of EP-204.

Component (test material was Oxoel 800)	Percent	Water Solubility (mg/L)	[Component] (mg/L) at 50 mg/L EP-204	EC_{50} (mg/L)
2,4-Diethyl-1,5-octanediol	51.9	44.4 (p)	26 (p)	7.1 (p)
2-Ethyl-1,3-hexanediol	9.1	4200 (e)	4.5 (p)	268 (p)
2-Ethylhexanol	12.6	880 (e)	6.3 (p)	39 (e)
Diethyloctanol	5-10	18.7 (p)	2.5-5 (p)	0.6 (p)
High-boiling components	20	Unknown Possibly < 1	10 (p)	?

Table 10. Analysis of EP-204 sample used for daphnia study.

In addition to solubility, persistence of these alcoholic components is another issue that should be considered in the aquatic-hazard assessment of EP-204. Aquatic toxicity and solubility have an inverse relationship for the neutral organic components of EP-204; thus, the more toxic materials are expected to be of lower solubility reducing their aquatic toxicity hazard. It has been determined that EP-204 is readily biodegradable and while this determination was for only one production run, this finding and structural examination of the most prevalent components suggest that none will be resistant to bacterial action in the environment.

Recommendation: No additional ecotoxicity studies are recommended. The available information fills the HPV required data elements.

Health Effects

An acute oral toxicity study has been conducted on commercial EP-204 (test substance Oxoel 800) showing an LD_{50} in male and female rates greater than 5000 mg/kg without indications of specific toxic effects (18). Several studies have been conducted on individual components of EP-204 that cover repeat dose, reproductive and developmental endpoints. Especially relevant are toxicity studies of 2-ethylhexanol and 2-ethyl-1,3-hexanediol.

2-Ethylhexanol is a high volume chemical used in the manufacture of plasticizers such as diethylhexyl phthalate and diethylhexyl adipate. As a result of the plasticizer end use and potential for consumer exposure, 2-ethylhexanol has been well studied toxicologically.

In the past, 2-ethyl-1,3-hexanediol was used commercially as an insect repellent and is still used today as a solvent in cosmetics. The pesticide registration was voluntarily withdrawn after a developmental toxicity study showed malformations in rat fetuses at maternally toxic doses. Because of this former use as an insect repellent and current use in cosmetics, this material has been fairly well studied regarding toxicity, especially by the dermal route. Since withdrawal of its pesticide registration and use as an insect repellent, fewer new studies have been reported.

2-Ethyl-1,3-hexanediol has been nominated to the NTP as a candidate for reproductive and developmental studies. Its current NTP status is "Deferred pending an evaluation of an industry study and EPA's risk management assessment". The safety of 2-ethyl-1,3-hexanediol as a solvent in cosmetics was reviewed for FDA by the Cosmetics Ingredients Review (CIR) Expert Panel and their published conclusion is "safe as used in concentrations up to five percent" (19).

Metabolism

Adsorption, distribution, metabolism and excretion are important processes that facilitate an understanding of the potential health effects of a material and allow the extrapolation of data among studies and routes of exposure. This is particularly true in the case of EP-204 where common metabolic routes, fates and inter-conversions of the individual EP-204 components justify the use of data from representative components to evaluate the health hazard of the commercial product.

It is postulated that most EP-204 components are metabolized by oxidation to a carboxylic acid and then either conjugated and excreted or are broken down fully by a series of oxidation reactions (primarily beta oxidation). Thus, after the initial oxidation of the alcohol by dehydrogenases, the fatty acid metabolism system treats the resulting carboxylic acids as fatty nutrients. The final products are carbon dioxide and acetyl-CoA with formation of ATP along the way. Several published studies support this hypothesis.

It is known that after oral administration, 80% of the absorbed 2-ethylhexanol is excreted in the urine and only about 6% is expired as carbon dioxide. In the rat, 2-ethylhexanol is initially rapidly oxidized to 2-ethylhexanoic acid and then apparently conjugated and filtered by the kidney faster than it can be metabolized via beta oxidation. Presumably, the carbon dioxide is formed primarily by beta oxidation of 2- ethylhexanoic acid. Evidence for beta oxidation also comes from the identification of small quantities of 2- and 4-heptanone in the urine, which are formed by a partial beta oxidation followed by decarboxylation rather than beta scission (20).

In a study of 2-ethyl-1,3-hexanediol metabolism, investigators were unable to detect any metabolites when 2-ethyl-1,3-hexanediol was fed to rabbits (21). This suggests that the metabolism of 2-ethyl-1,3-hexanediol via beta oxidation proceeds more readily than that of 2-ethylhexanol. Additional confirmation comes from a

pharmacokinetics study of (1,3-^{14}C)- 2-ethyl-1,3-hexanediol that was conducted following iv dosing of male Fischer 344 rats. Pharmacokinetic analyses of the plasma data indicated that there is dose linearity in the 1.5 to 150 mg/kg range, and that 2-ethyl-1,3-hexanediol is cleared from plasma in a bi-exponential manner according to first order transfer and elimination processes. The data show that 2-ethyl-1,3-hexanediol-derived radioactivity is rapidly distributed and then slowly eliminated probably as metabolites over a 48 hr period after a single iv injection. 2-Ethyl-1,3-hexanediol is not found in the urine as unchanged test material, which also indicates that this chemical is probably completely metabolized in the rat (22).

If the structures of 2-ethylhexanol and 2-ethyl-1,3-hexanediol are examined with regard to the biochemical events that are responsible for beta oxidation, this difference in elimination – primarily urinary excretion (2-ethylhexanol) versus complete metabolism (2-ethyl-1,3-hexanediol) - is logical. Figure 10 gives the structures of the EP-204 components 2-ethylhexanol and 2-ethyl-1,3-hexanediol. As beta-oxidation requires several distinct steps and as 2-ethyl-1,3-hexanediol has the beta carbon in an oxidized state already, it is well down the beta-oxidation pathway as it is absorbed. On the other hand, 2-ethylhexanol requires several metabolic steps before undergoing beta oxidation. As these steps require time and cofactors, there is more opportunity for renal filtration to remove a significant portion as the unchanged 2-ethylhexanol or its conjugated initial metabolite.

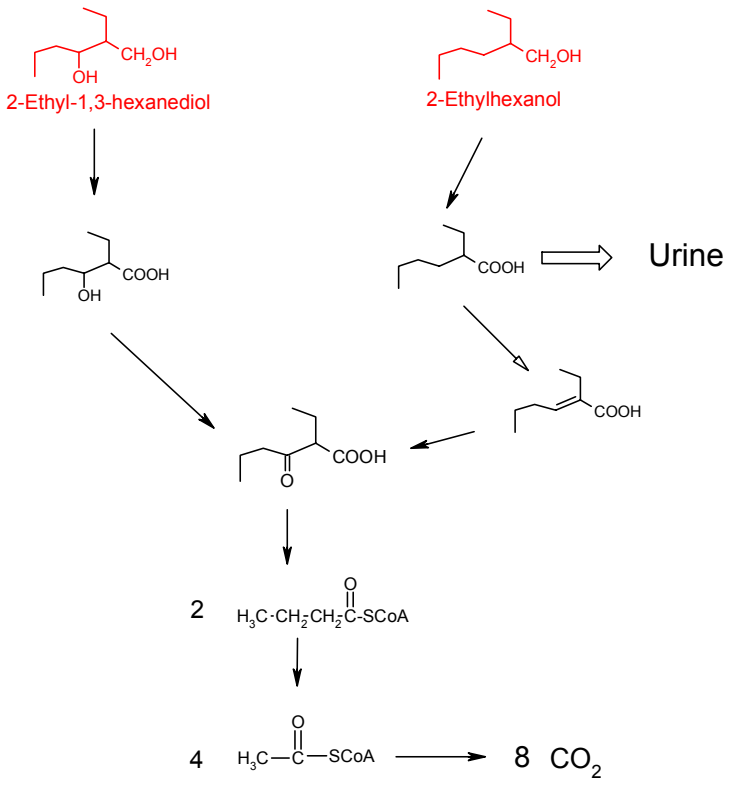

Figure 10. Major Excretion Routes for 2-Ethylhexanol and 2-Ethyl-1,3-hexanediol.

No information on the metabolism of higher congeners was located but based on the similarity in structure of these congeners with 2-ethyl-1,3-hexanediol, and their greater lipophilicity, it is anticipated that they compete favorably for beta oxidation rather than being excreted readily in the urine. It can be seen in Figure 11 that beta oxidation is an available option for the C-12 mono alcohol. Similarly, the C-12 diol (2,4-diethyl-1,5-octanediol) that was the major component of the EP-204 used in the daphnid test could be subject to beta oxidation; and it is pre-oxidized for the second round of beta oxidation. All of these metabolic schemes feed into the common intermediate 5-keto-2-ethylhexanoic acid that will undergo scission to two CoA conjugates of butyric acid, and on to acetyl CoA and finally carbon dioxide. The esters, acetals and ethers all will fit into this same metabolic scheme after hydrolysis or ether cleavage.

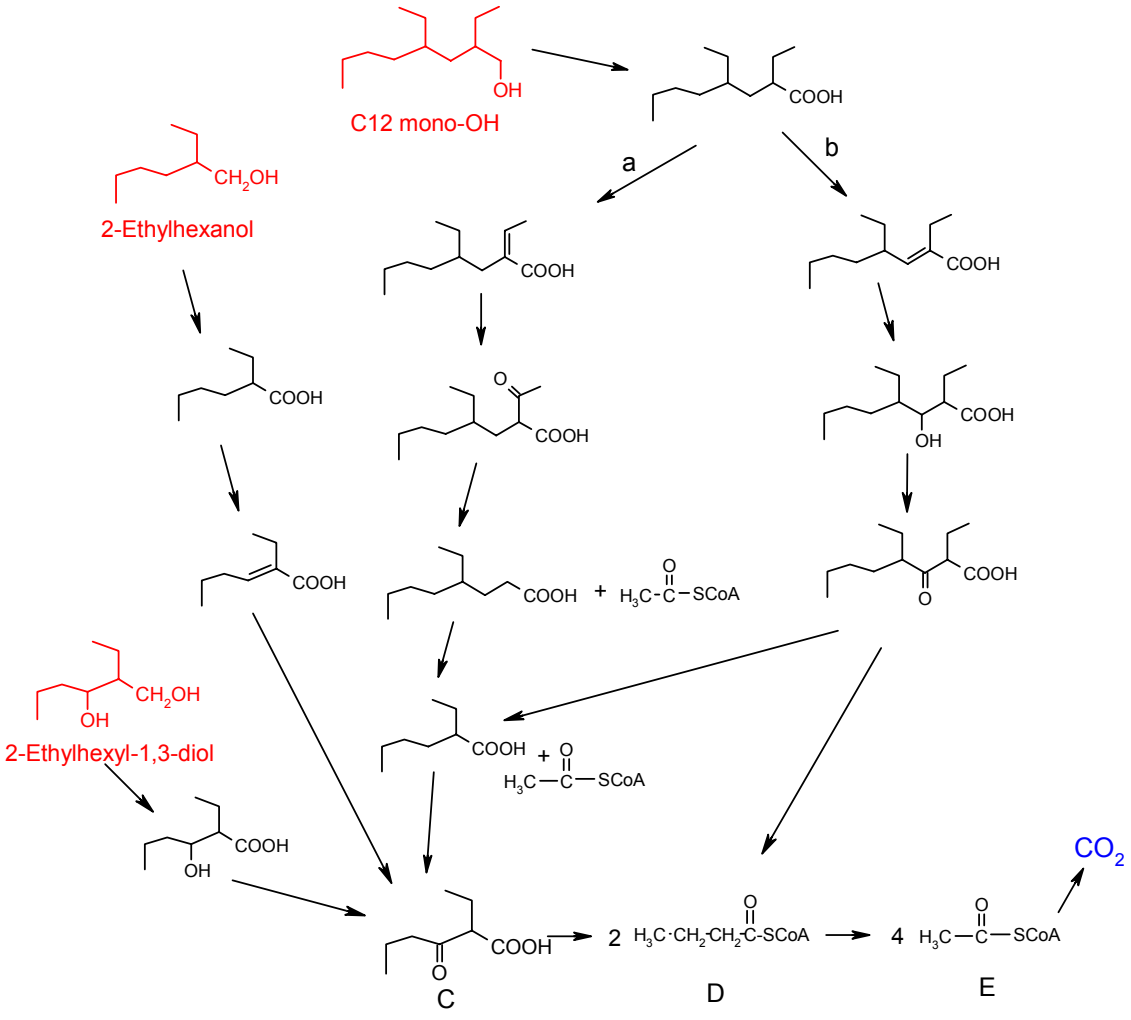

Figure 11. Common Metabolic Pathways of Major Components

In light of the similarity in structure of the most prevalent components of EP-204 and with the existence of a likely common metabolic path, the use of 2-ethylhexanol and 2-ethyl-1,3-hexanediol as surrogates for the entire mixture appears to be a logical and rational approach to understanding the hazard of EP-204.

Acute Toxicity

Oral Exposure

The oral LD_{50} of EP-204 (test substance was Oxoel) was determined in rats to be greater than 5,000 mg/kg. This study used groups of 5 Wistar rats of each sex and a "limit-test" design at a 5000-mg/kg dose level. Mortality was reported only in 2/5 females that died within 48-hours of dosing. Clinical signs were indicative of narcosis but were generally unremarkable. No chemically-related findings were reported at necropsy.

This low toxicity of the mixture is consistent with available data on the components. One of the components expected to be more toxic, 2-ethylhexanal, has been found to have an oral LD_{50} in rats between 2,626 and 3,730 mg/kg body weight (23). Likewise, the acute LD_{50} for 2-ethylhexenal is reported as 3,000 mg/kg in rats (24). The C-8 diol 2-ethyl-1,3-hexanediol has a reported oral LD_{50} of 1,300 mg/kg (25) and the acute-oral toxicity of 2-ethylhexanol in rats is low with an LD_{50} between 2049 and 7000 mg/kg (26).

The testing of a production sample of the actual chemical mixture and finding it less acutely toxic than some of its components provides some assurance that the components are not acting synergistically to produce excess acute toxicity. Although this observation does not preclude synergism in repeated-dose studies, it mitigates the concern regarding synergistic action.

Inhalation Exposure

Low volatility limits the vapor inhalation hazard for EP-204, which is essentially a distillation residue. Verification of this comes form an acute inhalation study conducted by BASF on Oxoel 800. In this study, six rats of each sex were exposed to a saturated vapor of the test material generated at 20° C for a period of 7 hours (27). The nominal concentration calculated from the flow rate and material loss was 0.11 mg/L. No animals died during exposure or in the 14-day observation period. No significant clinical signs were observed.

Available data on components support a low level of inhalation toxicity. A subchronic inhalation study using an essentially saturated concentration of 2-ethylhexanol vapors (120 ppm) has been conducted with no mortality after 13-weeks of exposure for 6 hours a day. The aldehyde components are potential inhalation hazards but they are such strong respiratory irritants that significant exposure of workers is considered unlikely (28).

Dermal Exposure

Although the acute dermal toxicity of EP-204 itself has not been reported, there is a report of a dermal test of "2-Ethylhexanol – Heavy Parts" tested under the same CAS No. The value given for the dermal LD_{50} of this material in the rat is > 1740 mg/kg (29). This value is consistent with the dermal LD_{50s} of potential 2-Ethylhexanol – Heavy Parts" components; however, neither compositional data of the tested material nor details of the study are available.

Available data from components confirm low dermal toxicity. The acute LD_{50} of 2-ethylhexanal in the rabbit has been reported to be 4235 mg/kg (23). The acute LD_{50} of 2-ethylhexenal in the guinea pig is greater than 20 ml/kg (30). 2-Ethylhexanol is reported to have a rabbit dermal LD_{50} between 1980 and >2600 mg/kg and a rat dermal LD50 >3000 mg/kg body weight (26). Pregnant rats all survived dermal application of 4 ml/kg of 2-ethylhexyl-1,3-diol for 10 consecutive days (31).

Recommendation: No additional acute toxicity studies are recommended. The available data fill the HPV required endpoints for acute toxicity. Although the available studies do not meet all the requirements of the current OECD guidelines in all cases, the weight of evidence shows that the oral, dermal and inhalation toxicity hazard is very low. Conduct of additional studies would not add significantly to our understanding of this material's toxicity and it is recommended that no additional acute toxicity studies be conducted.

Repeated Dose Toxicity

Oral Exposure

No repeated dose studies have been conducted on EP-204 itself, but several of its components have been investigated in repeated-dose studies. Based on the variety of possible structures contained in EP-204, the components and surrogates below are considered to be reasonably predictive of the repeated dose hazard of EP-204. Supporting this contention are metabolic data from 2-ethylhexanol that show complete metabolism of this substance to carbon dioxide and products of intermediary metabolism is possible (although urinary excretion of conjugates is normally an important means of excretion). As the C-8 aldehydes metabolically interconvert with 2-ethylhexanol, and as the higher homologs have the same basic structural components, all components are anticipated to be fully degraded in mammals by means of shared metabolic pathways initiated by oxidation to a carboxylic acid followed by a series of beta oxidations to four and two carbon compounds that are excreted (e.g. carbon dioxide) or incorporated into intermediary metabolism. The point being that these compounds can be handled by the body in a manner similar to nutrients without the build up of non-metabolizable or reactive structures; thus, adverse effects are considered unlikely after low-level exposure.

Recently conducted 13-week (32) and 2-year (33) studies are available for 2-ethylhexanol by oral gavage. In the 13-week study, groups of rats (10 animals of each sex) received daily oral gavage doses of 0, 25, 125, 250 or 500 mg/kg on 5 consecutive days per week for 13 weeks. Peroxisome proliferation was also determined in satellite groups of animals. The 500-mg/kg dose was associated with significant peroxisome proliferation and systemic toxicity as evidenced by a small but statistically significant ($p < 0.01$) reduction in body weight gain in rats of each sex. Target organs were the liver (increased organ weights with peroxisome proliferation and decreased peripheral lobular fatty infiltrate) and forestomach (acanthosis in the mucosa). There was also a slight increase in relative testis weight at 500 mg/kg but this was not correlated with any morphological changes. Reduced relative ovarian weights were seen at 250 mg/kg but did not occur at 500 mg/kg and were considered incidental, as there was no morphological correlate. It was concluded that 125 mg/kg was the NOEL based on treatment-related organ weight changes at 250 mg/kg (increased relative liver and kidney weights in males and females). The primary "adverse" effect was peroxisome proliferation noted in the 500 mg/kg males and females. Based on the results, the NOAEL was considered to be 250 mg/kg as the liver and kidney weight changes were probably adaptive since no histopathologic correlates were reported.

Chronic toxicity and carcinogenicity studies of 2-ethylhexanol in Fischer-344 rats were conducted at 50, 150, or 500 mg/kg/day 2-ethylhexanol by oral gavage for 24 months. Females showed a dose related increase in mortality, with 52% mortality at 500 mg/kg. Dose related reductions in weight gain were observed for both species. Increased focal lesions and lung discoloration was observed in rats at the 500 mg/kg dose. Significant increases in stomach, kidney and brain relative weights were observed in male rats at 150 mg/kg, with testis relative weight increase at the high dose. Female rats had significantly increased stomach, liver, kidney and brain relative weights at the 150 and 500 mg/kg doses. Microscopic examination showed changes in stomach, liver, lung, spleen, mesenteric and mandibular lymph nodes, kidney and prostrate at the 150 and 500 mg/kg doses. The 50 mg/kg dose produced a 6% increase in relative female stomach weight. The authors concluded that 2-ethylhexanol does not cause tumors in rats (33).

A 90-day subchronic inhalation study of 2-ethylhexanol has also been recently published (34). This study was performed on Wistar rats in accordance with OECD testing guidelines. Groups of 10 rats of each sex were exposed to 2-ethylhexanol vapor at concentrations of 15, 40 and 120 ppm (saturated vapor at 20° C) for 6 hours/day for 90 days. Controls were exposed to air under the same conditions. No substance-related adverse effects were observed for body weight, body weight gain, mortality, organ weights, clinical biochemistry and hematological parameters including clotting time. Cyanide-insensitive palmitoyl-CoA oxidation, a marker for peroxisome proliferation, was not elevated in this study. There were no findings related to the treatment with 2-ethylhexanol either at necropsy or at histological examination. The highest concentration tested under these conditions (120 ppm) was found to be the NOAEL for rats of each sex.

Other Components

The subchronic toxicity of 2-ethyl-1,3-hexanediol was evaluated using groups of rats (five of each sex) given doses of 0, 100, 300, or 1000 mg/kg-day, five days per week over a 29-day period (35). No effects were reported

with regard to mortality, clinical behavior, body weight, feed consumption, or serum chemistry. White blood cell counts, relative liver weights, and relative spleen weights were elevated in females receiving 300 or 1000 mg/kg-day, rats of each sex given 1000 mg/kg, and males given 1000 mg/kg, respectively. Platelet counts were lower in females in the 1000 mg/kg group. The NOAEL was considered to be 100 mg/kg.

The dermal subchronic toxicity of 2-ethyl-1,3-hexanediol has been studied in rats (36). Undiluted test material was applied to the skin of eight-week old Fischer-344-rats at daily doses of 0, 0.5, 2.0, or 4.0 ml/kg, 5 days a week for 9 days or 13 weeks. Selected rats were killed on the last day of the 13-week study, on the tenth day of the 9-day study, or 3 to 5 days or 6 weeks after the last dose of the 13-week study and necropsied. No clinical signs of systemic toxicity or skin irritation were seen in either the 9-day or 13 week study. Slight decreases in body weight gain were reported for the 4.0 ml/kg group males in the 9-day study and for the 4.0 ml/kg rats of each sex in the 13-week study. No treatment related changes in hematology or serum and urinary chemistry were seen. The only treatment-related organ or tissue change identified was a slight increase in relative liver weight ~~seen~~ in the 4.0 ml/kg females after 9 days of treatment and the 4.0 ml/kg males after 13 weeks of treatment. The authors concluded that repeated skin applications of undiluted 2-ethyl-1,3-hexanediol did not cause local skin reactions or systemic toxicity in rats. The slight increases in relative liver weight seen in high dose females in the 9-day study and high dose males in the 13-week study probably reflect an adaptive hypertrophy associated with the metabolism of test substance since these weight increases were not accompanied by any biochemical or morphological evidence of liver injury. The 9-day and 13-week NOAEL was considered to be 4.0 ml/kg.

Repeated administration of 2-ethylhexanal in the diet of rats for three weeks, at about 2,000 mg/kg-day, leads to moderate peroxisome proliferation in the liver as well as hypolipidemia and hepatomegaly (37). An OECD 412 Guideline inhalation study has been conducted on 2-ethylhexanal but the available information giving the results is too limited to draw any conclusions (38).

In summary, available studies of major components of EP-204 have revealed that the materials can be completely metabolized by the body as fatty nutrients with the only effect being an adaptive stimulation of the liver. It is anticipated that all structurally related components will share similar metabolic fates causing liver stimulation (peroxisome proliferation and hypertrophy) as hallmark effects.

Recommendation: No additional repeated-dose studies are recommended. The available data adequately fill the HPV required data element for repeated-dose toxicity.

Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points, one sensitive to point mutation and one sensitive to chromosomal aberrations. In the case of this material, adequate tests have been conducted on several components of the mixture (indicating low genotoxic hazard) but not on the mixture as a whole to cover either of these endpoints.

Component	Test System	Result	Ref
2-Ethylhexanol	Ames Test [RS]	neg	39
	Ames Tests (multiple)	neg	40, 41, 42, & others
	In vitro CA [RS]	neg	39
	In vitro SCE	neg	39
	HGPRT assay (CHO cells)	neg	43
	Mouse lymphoma assay	neg	44
	Mouse micronucleus (in vivo)	neg	45
	Many others	neg	46
2-Ethyl-1,3-hexanediol	Ames test (multiple)	neg	47, 48, 49
	Gene mutations in CHO cells	neg	47
	SCE in CHO cells	neg	47
	Mouse lymphoma	+/-	48
	CA in CHO cells	+/-	47
	Mouse micronucleus (in vivo)	neg	48
2-Ethylhexenal	Ames test	neg	50, 51
2-Ethylhexanal	Ames test	neg	52
Butyraldehyde	Ames test (multiple)	neg	53, 54, 55, 56
	CA in CHO cells	neg	57
	HGPRT	pos	58
	SCE in CHO cells	pos	57
	SCE in human lymphocytes	neg	59
	Drosophila SLRL test	neg	60, 61

CA= chromosome aberration test, SCE = sister chromatid exchange test, SLRL = sex-linked recessive lethal, [RS] = robust summary prepared

Table 11. Genotoxicity of EP-202 Components

Genetic Toxicology in vivo

Some *in vivo* genotoxicity studies have been conducted on the components of EP-204 and representative results are shown in Table 11. The *in vivo* studies support the *in vitro* data indicating a minimal genotoxic hazard for EP-204.

Recommendation: No additional genetic toxicity testing is recommended as the SIDS requirement for genetic testing is filled by data on the individual components.

Reproductive Toxicity

Although no studies of the EP-204 mixture have been conducted, some of the components have been evaluated and found to have little capacity to produce specific reproductive toxicity. As is the case for most of the health effects studies of EP-204, 2-ethylhexanol is considered to be the most appropriate surrogate for this mixture.

Although a proper guideline-like reproductive toxicity study of 2-ethylhexanol was not found, there are modern 13-week (32) and chronic studies (33) of this material in which the reproductive organs were evaluated. In the case of the 13-week study, gavage dose levels were 0, 25, 125, 250 or 500 mg/kg. The reproductive-organ evaluation showed that aside from an increase in testes weights at the high dose unaccompanied by histological changes, there were no effects on reproductive organs. Results from the chronic study are similar. In addition to these evaluations, there is a dosed-feed developmental toxicity study of 2-ethylhexanol that was conducted in mice at 0, 17, 60 or 194 mg/kg-day (vide post) by the NTP with negative results (65, 66). This combination of lack of effects on reproductive organs combined with a modern developmental toxicity study indicating no developmental effects fulfills the HPV reproductive toxicity endpoint.

Another surrogate chemical for use in assessing the reproductive toxicity of EP-204 is diethylhexyl adipate (DEHA, the diester of adipic acid with 2-ethylhexanol). DEHA is known to be well absorbed by rodents and primates and rapidly converted (both in the gut and after systemic absorption) to 2-ethylhexanol and adipic acid (62). Like 2-ethylhexanol, adipic acid is metabolized via beta-oxidation but metabolized to succinic and acetic acids, and subsequently to other normal intermediary metabolites (63). In a one-generation reproductive study (64), groups of Wistar-derived rats (15 males/dose; 30 females/dose) were administered DEHA in their diets at a level of 0, 28, 170, or 1080 mg/kg/day. After 10 weeks on the diet, the animals were mated to produce one-generation of offspring that was reared to day-36 post partum. Test substance was administered continuously throughout the study (approximately 18-19 weeks of exposure). No effects were seen on male or female fertility. At the highest dose, however, there was a reduction in the body weight gain of the dams during gestation; an increase in liver weight in both male and female parents; and reductions in offspring weight gain, total litter weight, and litter size. The NOAEL and LOAEL for this study were also 170 and 1080 mg/kg/day DEHA [about 120 and 760 mg/kg/day 2-ethylhexanol], respectively. In summary, DEHA administration to male and female rats did not interfere with fertility, even at parentally toxic doses.

Reproductive effects have been adequately assessed through the combination of the negative reproductive and developmental toxicity studies on components of this complex mixture and the subchronic study. Conduct of additional studies on a low-exposure variable mixture would not be a sufficient contribution to warrant use of animals for testing.

Recommendation: No additional reproductive testing is recommended. The available data on components provided sufficient information for informed hazard determination.

Developmental Toxicity

EP-204, as a specific mixture, has not been tested for developmental toxicity but major components have been evaluated and found to have little capacity to produce specific developmental toxicity. As is the case for most of the health effects studies of EP-204, 2-ethylhexanol is considered to be the most appropriate surrogate for this mixture.

The National Toxicology Program has conducted a developmental toxicity study on 2-ethylhexanol in pregnant Swiss mice (65, 66). In this study, groups of 28 pregnant Swiss (CD-1) mice were treated with 2-ethylhexanol (2EH) in feed at 0, 90, 300 or 900 ppm in feed (corresponding to 0, 17, 60, 194 mg/kg-day) in a microencapsulated form. At sacrifice on gestational-day 17, the number of ovarian corpora lutea and uterine implantation sites, including resorptions, and dead or live fetuses, were recorded. Live and dead fetuses were weighed. Live fetuses were sexed and examined for external, visceral and skeletal malformations and variations. No adverse effects on development were reported; however, no maternal toxicity was observed. The NOAEL for developmental and maternal toxicity was > 194 mg/kg.

Dermally administered 2-ethylhexanol was evaluated for developmental toxicity using three groups of 25 pregnant female Fischer 344 rats treated cutaneously with 2-ethylhexanol at dose levels of 0, 0.3, 1.0, or 3.0 ml/kg-day for 6 hours per day on gestation days 6 through 15 (67). No treatment-related maternal deaths or early pregnancy losses were seen in the treatment groups, but maternal weight gain was significantly reduced during gestation day 6 through 9 in the high-dose animals. Exfoliation and crusting were seen at treatment sites at all dose levels and erythema at dose levels of 1.0 and 3.0 ml/kg-day. Low-dose groups, showed an increase in postimplantation loss, decreased litter size, and reduced fetal body weights but this was not observed in the high-dose group; thus a dose-response relationship was not observed for these parameters. There were no significant increases in incidence of malformations in the 2-ethylhexanol groups relative to the sham treatment group. It can be concluded that 2-ethylhexanol has no activity as a developmental toxin by the dermal route in rats. The NOAEL's are considered to be: developmental 3 ml/kg-day, maternal systemic toxicity 1.0 ml/kg-day, and no NOAEL was identified for maternal dermal effects.

As discussed earlier (vide ante), another surrogate chemical for use in assessing the toxicity of EP-204 is diethylhexyl adipate (DEHA, the diester of adipic acid with 2-ethylhexanol). DEHA is rapidly absorbed by rodents and converted to 2-ethylhexanol (68). In a one-generation reproductive study (69), groups of Wistar-derived rats (15 males/dose; 30 females/dose) were administered DEHA in their diets (0, 28, 170, or 1080 mg/kg/day). After 10 weeks on the diet, the animals were mated to produce one-generation of offspring that was reared to day-36 post partum. Test substance was administered continuously throughout the study (approximately 18-19 weeks of exposure). No effects were seen on male or female fertility. At the highest dose, however, there was a reduction in the body weight gain of the dams during gestation; an increase in liver weight in both male and female parents; and reductions in offspring weight gain, total litter weight, and litter size. In summary, DEHA administration to pregnant female rats was associated with only minor manifestations of fetal toxicity at maternally toxic doses. The developmental and maternal NOAEL were 170 mg/kg-day DEHA (~ 120 mg/kg/day 2-ethylhexanol).

2-Ethyl-1,3-hexanediol was studied in an oral-gavage developmental toxicity study sponsored by Kodak (70). In this study, developmental toxicity was evaluated in groups of pregnant Charles River CD rats administered test material by gavage at dose levels of 0, 500, 1000, 2000, or 4000 mg/kg on days 6-15 of gestation. Surviving rats were sacrificed on gestation day 20 for evaluation of the gestational products. One dam at 2000 and seven dams at 4000 mg/kg died on test. Signs of maternal toxicity were observed at 2000 mg/kg and above and included: weakness; dehydration; respiratory problems; abnormal gaits; nasal discharge; porphyrin tears; diarrhea; reduced fecal volume; hypothermia; reduced mean body weights (at all dose levels); significantly increased mean relative liver weights (2000 mg/kg); necrosis of the glandular gastric mucosa; excessive mucus secretion in the cecum; and atrophy of the thymus and adipose tissues. Significantly increased early resorptions were observed at 2000 mg/kg. Fetal malformations were increased for the following at 2000 mg/kg: missing tails; abnormal curvature of the hindlimbs; arthrogyroposis; shortened trunk in the lumbar region; umbilical hernia; and rudimentary (filamentous) tails (at 500, 1000, and 2000 mg/kg). There were no compound-related changes in mean number of corpora lutea, number of implantation sites, viable fetuses/litter, or pre-implantation losses. It is concluded that administration of test material was associated with developmental toxicity at maternally toxic doses. Neither maternal nor developmental NOAELs were identified; however 1000 mg/kg appears to be a developmental NOAEL for major malformations.

2-Ethyl-1,3-hexanediol was also studied in a dermal-administration developmental toxicity study. In this study, developmental toxicity was evaluated in groups of 25 timed-pregnant CD rats administered test material by cutaneous application of undiluted test material at dosages of 1.0, 2.0 and 4.0 ml/kg-day for 6 hr/day under occlusion on gestational days 6-15 inclusive (31). A control group was treated with water using the same exposure regimen. Maternal toxicity was present at 4.0 ml/kg-day (reduced body weight gains and mild skin irritation that were not statistically significant, and statistically significant increased liver weight), and also minimally at 1.0 and 2.0 ml/kg/day (mild skin irritation and slight but significant increase in relative liver weight). At 4.0 ml/kg-day there was one visceral malformation (unilateral hydroureter), increased incidences of three visceral variants (atelectasis, dilated lateral cerebral ventricle, and bilateral dilated ureter), and 13 skeletal variants affecting several skeletal districts. At 2.0 mL/kg/day no malformations were observed, but the incidence of two

visceral variants (dilated lateral cerebral ventricle and bilateral dilated ureter) and one skeletal variant (reduced caudal segments) was increased. The authors concluded that, under the conditions of this study, 2-ethyl-1,3-hexane-1,3-diol is considered a weak developmental toxicant at 4.0 or 2.0 ml/kg-day, and 1 ml/kg-day was a "no-observed effect level" for developmental toxicity.

Both the oral and the dermal developmental toxicity studies of 2-ethyl-1,3-hexanediol are consistent with this material not having developmental toxicity below maternally toxic doses.

In summary, major components of EP-204 have been tested for developmental toxicity and found to produce adverse fetal effects only in the presence of maternal toxicity. Results from these major components are considered to be representative of the developmental toxicity of EP-204 as a mixture.

Recommendation: No additional developmental toxicity testing is required as the available data are sufficient to assess the developmental toxicity of the most volatile component of this material. Conduct of additional studies on a low-exposure variable mixture would not be a significant enough contribution to warrant the use of experimental animals in light of the available information on major components and the composition of EP-204.

Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, it is concluded that the available information on major components of the mixture EP-204 and on commercial EP-204 itself meet all requirements for physicochemical parameters, fate information, aquatic toxicity and mammalian toxicity. Although the available studies do not meet all the requirements of the current OECD guidelines in all cases, taken together the information provides a reliable hazard assessment.

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